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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/992,443
Filing Date: November 16, 2001
Appellant(s): LEVITSKY ET AL.

Carol Larcher

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 24, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

This appeal involves claims 1-14, 17-28, 40-47, and 50-53.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct with regard to issues (i), (ii), and (iii). The appellant's statement of the issues in the brief is

incorrect with regard to issue (iv). The changes are as follows: The appellant did not dispute the rejection under the judicially created doctrine of obviousness-type double patenting listed as issue (iv). The appellant indicated, "upon an indication of allowable subject matter, Appellants will submit a terminal disclaimer".

Upon further consideration, the following rejections are withdrawn:

1. Previous rejections of Claims 4, 8, 13, 14, 18, 21, 42, 43, 46, 51, and 53 under 35 U.S.C. § 112, 1st paragraph for matters of written description and enablement, are withdrawn.
2. Previous rejection of Claims 1-14, 17-22, 26, 27, 40-47, and 50-53 under 35 U.S.C. § 112, 2nd paragraph, is withdrawn
3. Previous rejection of Claims 1, 5, 7, 17, 20, 22-24, 28, 40, 41, 44, 45, 50, and 52 under 35 U.S.C. 103(a), is withdrawn.

Currently, Claims 1-3, 5-7, 9-12, 17, 19, 20, 22-28, 40, 41, 44-47, 50, 52 stand rejected under 35 U.S.C. 112, first paragraph for matters of lacking written description and enablement; and Claims 1-14, 17-28, 40-47, and 50-53 stand rejected under the judicially created doctrine of obviousness-type double patenting.

(7) Grouping of Claims

Appellant's brief includes a statement that for each ground of rejection, the rejected claims stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5637483	Dranoff et al.	6/10/1997
6348352	Shepard et al.	2/19/2002
6521449	Polack et al.	2/18/2003
6464973	Levitsky et al.	10/15/2002

Ferrone et al, Immunology Today 1995;16:87-94.

Janeway Jr. et al, Immunobiology, 2001.

Kageshita et al, Cancer Res. 1993 Jul 15;53(14):3349-54

Klein et al, Int J Cancer 1976:18:421-31.

Thomas et al, Hum Gene Ther 1998;9:835-43.

Wang et al, J Clin Invest 1993;91:684-92.

Wang et al, Tissue Antigens 1996 ;47 :382-90.

Winchester et al, PNAS 1978 Dec;75:6235-9.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-3, 5-7, 9-12, 17, 19, 20, 22-28, 40, 41, 44-47, 50, 52 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Please note the previous rejection of claims 4, 8, 13, 14, 18, 21, 42, 43, 46, 51, and 53 is withdrawn, because these claims are drawn to a specific human cell line K562, and methods of making and using such, which relates to the subject matter claimed in U.S. patent 6,464,973.

Given the broadest reasonable interpretation, the claims embrace numerous universal bystander human cell lines, each is made from a cell line of human origin, and naturally lacks both major histocompatibility class I (MHC-I) antigens and major histocompatibility class II (MHC-II) antigens. The standing claims are rejected because the specification fails to provide an adequate written description for the *starting materials* necessary to make the claimed *genus* of genetically modified universal bystander human cell lines expressing GM-CSF.

Concerning the term "naturally" in the claims, although the specification does not explicitly define the term, the term was used in the specification opposite to "modified" [by hands of man]. Thus, the phrase "naturally lacks MHC-I and MHC-II antigens" encompasses both cell lines that never had MHC-I and MHC-II antigens, and cell lines that lost MHC-I and MHC-II antigens due to cancerous mutation. As such, what human cell lines are embraced by the instant claims? For cells that never have had said antigens, it is well known in the art of the immunology that all nucleated cells naturally and constitutively express MHC-class I molecule, whereas immune system cells such

as dendritic cells, B-lymphocytes, and macrophages naturally express MHC-class II molecule (*Janeway Jr. et al*, Immunobiology, 2001). Accordingly, it appears only red blood cells (RBCs) meet claim limitation, i.e. they do not possess nuclei and are not immune system cells, and thus they never have and would naturally lack MHC-I and MHC-II antigens. On the other hand, in light of the specification, the required human cell lines that naturally lack MHC-I and MHC-II antigens also encompass cancer cell lines that lost MHC-I and MHC-II antigens due to cancerous mutation.

As an initial matter, the methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Concerning the first approach, the specification fails to describe a RBC cell line or any normal human cell line naturally lacks MHC-I & II antigens, neither a discovery by the appellant nor known to the art of record. Further since the red blood cells lacking a nucleus, (which usually is the target site of the genetic modification), the specification fails to teach whether the red blood cells possess the machinery necessary for

expressing an exogenous gene, and to the extend that GM-CSF could be efficiently expressed at levels >500-1000ng GM-CSF/10^6 cells/24 hours as required by the claims. Accordingly, the specification fails to disclose a cell line that is truly and naturally lacking MHC-I and MHC-II antigens. The specification does describe an actual reduction to practice of a human cell line that lacks both MHC-I and MHC-II antigens due to cancerous mutation, i.e. K562 cells derived from a patient with blast crisis of chronic myeloid leukemia, and the modified K562 cells expressing GM-CSF (a universal bystander human cell line), for which appellants have obtained a patent, USP 6,464,973. However, out of hundreds if not thousands of tumor cell lines, for which the surface markers may extremely vary and new mutations may constantly occur, K562 is the only cell line, disclosed by the appellant either in the specification or in the subsequently submitted references, proven to be lacking both MHC-I and MHC-II antigens. In view of such, the disclosure fails to provide a representative species for the claimed genus, i.e. human cell lines that *never had* or *lost* MHC-I and MHC-II antigens. The Revised Interim Guideline for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement (Federal Register/ Vol 66. No. 4, Friday, January 5, 2001) states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE

GENUS" (Column 2, page 71436, emphasis added). Hence, it is concluded that K562 alone is not sufficient enumeration of representative species of a genus, and the specification fails to use this approach describing the broadly claimed invention.

Concerning the second approach, the specification fails to provide any drawing that evidences the claimed genus of human cell lines naturally lacking both MHC-I and MHC-II, and thus evidences the claimed genus is in possession of the appellants at the time this application was filed. Hence, the specification fails to use this approach describing the broadly claimed invention.

Concerning the third approach, the specification fails to set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed genus because beyond the exemplified k562 cells, the specification is silent with respect to the identifying characteristics of human cell lines that naturally lack both MHC-I and MHC-II. The specification mentioned the term "naturally" twice in the entire 20-page specification at page 5, line 3, and page 6, line 30, and each time it simply states the present invention provides an universal bystander cell line that naturally lacks MHC-I and MHC-II antigens. The specification fails to provide other descriptions either by exemplification, or by distinguishing identifying characteristics with respect to what type of cell lines naturally lack both MHC-I and MHC-II, and whether such cell lines are well-known in the art beyond the K562 cell line. The specification fails to provide a single human cell line that never had MHC-I and MHC-II antigens and the specification provide only a single human cell line that lost MHC-I and MHC-II antigens due to

cancerous mutations, yet claims encompass a genus of universal bystander human cell lines, made from a genus of human cell lines naturally lacking both MHC-I and MHC-II antigens. Appellants are reminded adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or using it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. representative species of specific human cell lines that naturally lack both MHC-I and MHC-II, which provide the means for practicing the invention. Accordingly, beyond the circular teaching, the specification fails to use this approach describing the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION *OF THE INVENTION*. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of above considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention because it does not provide adequate written description for the broadly claimed genus of universal bystander human cell lines.

To the extent that the claimed methods are not adequately described in the instant disclosure, claims 1-3, 5-7, 9-12, 17, 19, 20, 22-28, 40, 41, 44-47, 50, 52 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been adequately described, and which is not conventional in the art.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature of the claims relative to the state of the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are drawn to a genus of universal bystander human cell lines derived from a genus of human cell lines that either never had MHC-I & -II antigens or lost them due to cancerous mutations. However, the specification fails to disclose a single human cell line that never had MHC-I & -II antigens, and the disclosure can only point to a single cell line that lost MHC-I & -II antigens during the blast crisis of chronic myeloid leukemia. Further, the specification fails to provide adequate guidance with respect to how to find additional cell lines that belong to the claimed genus. For example, the specification fails to teach what normal human cell lines may possibly never have MHC-I & -II antigens, and what type of tumor cell lines may have higher possibilities of losing both MHC-I & -II antigens. Claim 2 recites traits the candidate human cell line lacks, but the specification fails to teach where to start the search to find the human cell line that lacks the recited traits, and it fails to teach what traits the candidate human cell line possesses.

It is noted that the K562 cell line was established almost 30 years ago (*Klein et al*), given the limited guidance provided by the specification, given the knowledge of the skilled in the art, and given the cycle of discovery from K562, it is unpredictable the amount of work and time it would take for one skilled to search and unearth another cell line like K562 that qualifies as another member of the genus, it appears that such search is unduly burdensome to the skilled intending to practice the invention. Accordingly, in view of the state of the art coupled with the guidance provided by the specification, it would have required undue experimentation for the skilled artisan to

identify and discover other cell lines that lack both MHC-I and MHC-II antigens, which are required for the practice of the claimed invention.

The court has stated "LAW REQUIRES THAT THE DISCLOSURE IN APPLICATION SHALL INFORM THOSE SKILLED IN THE ART HOW TO USE APPLICANT'S ALLEGED DISCOVERY, NOT HOW TO FIND OUT HOW TO USE IT FOR THEMSELVES" *In re Gardner* 166 USPQ 138 (CCPA) 1970. The court has determined that in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Goodman, 29 USPQ2d 2010 (CA FC 1993); In re Fisher, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT."

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, it would have required undue experimentation as it is broadly claimed.

Claims 1-14, 17-28, 40-47, and 50-53 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 6,464,973. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims encompass the claims of the cited patent.

The claims of present application and the claims of the cited patent are each drawn to a universal bystander cell line which lacks MHC-I and MHC-II antigen, derives from a human cell line, and has been modified to express GM-CSF at about 500 ng or greater GM-CSF/10^6 cells/24 hours. The claims of present application and the cited patent are not patentably distinct from each other also because they are each drawn to a method of making a universal GM-CSF-expressing bystander cell line, and a method of using such cell lines for cancer immune therapy.

The product/processes of the present application and the cited patent differ one from the other in that the claims of the cited patent is drawn to a particular cell line k562 and the methods of making/using such, whereas instant claims are drawn to a genus of the modified universal bystander cell lines, the method of making such, and the method of using such for immune therapy. However, the instant claims encompass the claims of the cited patent.

Therefore, the claims as written are co-extensive.

(11) Response to Argument

Appellant's arguments have been addressed in the order in which they have been presented in the appellant's appeal brief.

Arguments concerning rejections of Claims 1-3, 5-7, 9-12, 17, 19, 20, 22-28, 40, 41, 50, 52 under 35 U.S.C. § 112, 1st paragraph, Written Description Requirement.

As an initial matter, it is noted that the appellant presented disproportional amount of arguments regarding how to interpret the term "naturally", and how case law "*Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999)" should be interpreted. Appellants then allege that the rejection to the term is the only and hence ill-founded basis upon which the Examiner can continue to maintain a rejection for lack of written description (Brief, page 6, 1st paragraph).

In response, if the allegation is true as asserted by the appellant, the brief should be stopped at page 6, 1st paragraph. Then it is unclear why appellants need to write pages 6 through 9 addressing issues under 35 U.S.C. § 112, 1st paragraph. In fact, the arguments in pages 4 through 6 are more relevant to the rejection under 35 U.S.C. § 112, 2nd paragraph, and are moot because the rejection under 35 U.S.C. § 112, 2nd paragraph is now withdrawn. Nevertheless, it is noteworthy that the Examiner has repeatedly pointed out (in the final Office action, 2nd paragraph, page 3, and Advisory, 2nd paragraph) that the only reason this issue has been raised under 35 U.S.C. § 112,

1st paragraph is because given the ordinary and customary meaning, the limitation encompasses cell lines that truly naturally lack both MHC-I and MHC-II antigens, i.e. in the words of appellant as recited in the Brief, "*it never had MHC-I and MHC-II antigens*" (Brief, page 5, mid-section of the 2nd paragraph). Apparently, "Cell lines that never had both MHC-I and MHC-II" may not be the only type of cell lines that naturally lack MHC-I and MHC-II antigens, but they should at least be an important component what the claim limitation encompasses, i.e. one of the two components for the types of cell lines that naturally lack both MHC-I and MHC-II according to what appellants interpret the phrase. Thus, it is proper to request the specification to provide an adequate written description for the important component of the claim limitation, i.e. cell lines that never had MHC-I and MHC-II antigens. Since, as indicated *supra*, the specification is completely silent in this aspect, it fails to provide adequate written description for the claimed invention.

The appellants then argue (Brief, page 6, 3rd paragraph) that they have disclosed the K562 cell line, and numerous examples of such cell lines were known in the art prior to the instant priority date, including Wang et al (1993), Ferrone et al, Kageshita et al, and Wang et al (1996).

In response, the Office has provided analysis regarding these references and concluded that the references provided loss of MHC-I due to cancerous mutation, but none of the references teaches a cell line that confirmed lacking both MHC-I and MHC-II antigens (See for example, pages 4-6 of paper No. 7, and pages 4-6 of the Office action mailed 12/17/03, the contents of which will be reiterated below). The following is

a list of the references cited by the appellants, what each one teaches, and whether it provides support for the appellant's assertion that "Appellants have found numerous other examples of cell lines that lack MHC-I and MHC-II antigen".

Wang et al (J Clin Invest 1993;91:684-92) teach melanoma cell line SK-MEL-33, which lost MHC-class I expression due to a mutation that leads to a reading frame shift in beta2-microglobulin mRNA. However, the Office provided evidence (*Winchester et al* (PNAS 1978 Dec;75:6235-9) indicating that SK-MEL-33 cells do not lack MHC-II antigen. *Winchester et al* report that widespread expression of Ia molecule (a type of MHC-II antigen) was found on malignant melanoma lines (last paragraph of left column, page 6235). Particularly, they teach that MHC-II antigen (Ia Ag) is expressed in 100% of SK-MEL-33 melanoma cells (table 1). Thus, the art of record evidences that SK-MEL-33 cells taught by *Wang et al* do not meet claim limitation, because they lack MHC-I antigen but not both MHC-I and MHC-II. Thus, this reference does not provide support for the appellants' assertion that "*Appellants have found numerous other examples of cell lines that lack MHC-I and MHC-II antigen*".

Ferrone et al (Immunol Today 1995;16:487-94) teach that approximately 16% of primary, 58% of metastatic melanoma cells, and 10% melanoma cell lines lack or have reduced levels of class I expression. *Ferrone et al* referred to *Winchester et al* and teach that many melanoma cells were found to express class II antigens. In *Winchester*'s own words, "THE PRESENT STUDY WAS DIRECTED PRIMARILY AT DETERMINING THE OCCURRENCE OF IA ANTIGENS ON VARIOUS CELL LINES DERIVED FROM DIFFERENT MALIGANCIES. THE CHIEF FINDING WAS THE WIDESPREAD OCCURRENCE OF THESE MOLECULES ON MALIGNANT

MELANOMA LINES" (2nd paragraph, page 6235). Apparently, *Ferrone et al* do not teach whether any one of the 10% melanoma cell lines happen to lack both MHC-I and II, *Ferrone et al* only teach the probabilities of MHC-I and MHC-II antigen expression on melanoma cell lines, i.e. 10% of melanoma cell line would lost MHC-I antigen, but widespread melanoma cells express MHC-II antigen. In table 2 of *Winchester et al,* six of ten melanoma cell lines expressing MHC-II in 100% of the tumor cells, and the remaining four lines expressing MHC-II in varying percentages of cells (2-35%). Hence, *Ferrone* reference does not provide any support indicating that it is known in the art that at least one of the melanoma cell line lacks both MHC-I and -II antigens. Thus, this reference does not provide support for the appellant's assertion that "*Appellants have found numerous other examples of cell lines that lack MHC-I and MHC-II antigen*".

Kageshita et al (Cancer Res. 1993 Jul 15;53(14):3349-54) teach MHC-I loss in 21% of the 14 primary and 44% of the 9 metastatic lesions tested. The reference does not provide a human cell line, nor cells that lack both MHC-I and MHC-II antigens. Thus, this reference does not provide support for the appellant's assertion that "*Appellants have found numerous other examples of cell lines that lack MHC-I and MHC-II antigen*".

Wang et al (Tissue Antigens 1996;47:382-90) reference is an abstract. It describes an extension of the *Wang et al* (1993) study, i.e. characterizing the molecular and functional phenotypes of the melanoma cell line that lack MHC-I expression, it does not disclose a cell line that lacks both MHC-I and MHC-II. Thus, this reference does not provide support for the appellant's assertion that "*Appellants have found numerous other examples of cell lines that lack MHC-I and MHC-II antigen*".

From the analysis *supra*, it is clear that despite the appellant submitted more references during the course of prosecution, as an attempt to prove that such cell lines are known in the art, the only cell line proven to be lacking both MHC-I and MHC-II antigens is still the K562. Hence, none of the references cited by appellants provides support for the assertion that "*Appellants have found numerous other examples of cell lines that lack MHC-I and MHC-II antigen*". Therefore, the arguments following that assertion are ill founded.

In a related issue, the appellants later argued in page 9 of the Brief (2nd paragraph), SK-MEL-33 cell line does not lack both MHC-I and MHC-II can be explained by differences in subclones, but it does not detract from the other examples of cell lines. In response, from the above analysis, none of the examples discloses a human cell line naturally lacking both MHC-I and MHC-II antigens, thus there is nothing on record to detract from. Appellants failed to provide any evidence showing the presence of the recited subclones that differ in MHC-II expression compared to the teaching of *Winchester et al*, thus the specification fails to provide an adequate written description for the claimed genus.

Appellants then cited case law "*Amgen Inc. v. Hoechst Marion Roussel, Inc.* 314 F.3d 1313 (Fed. Cir. 2003)", and argued that claim terms directed to cell lines known in the art, convey sufficient "information concerning their identity such that one of ordinary skill in the art could visualize or recognize the identity of the members of the genus. Appellants concluded that whether or not there is a red blood cell line is of no import. Likewise, the fact that tumor cell lines may vary widely in cell-surface is of no import,

because cell lines lacking MHC-I and MHC-II are known in the art (Brief, paragraph bridging pages 6-7). Applicants also argue the case law cited by the Examiner such as *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997) do not apply because cell lines lacking MHC-I and MHC-II are known in the art (Brief, 1st & 4th paragraphs, page 7).

In response, it is noted that according to the evidence and analysis *supra* discussed in detail in the immediate preceding section, contrary to the appellant's assertion, the genus of cell lines that lack both MHC-I and MHC-II antigens are not well known in the art prior to the instant priority date. Thus, when specification fails to disclose a single cell line that never had MHC-I and MHC-II antigens, it is an important indication that the specification has failed to meet the written description requirement set forth under this provision; and when specification fails to disclose a single tumor cell line beyond K562, it is another important indication that the specification has failed to meet the written description requirement set forth under this provision.

In this regard, the court has stated that: "IN CHEMICAL CASE WHERE APPLICANT DISCLOSES THAT ONE SPECIES OF A CLASS OF CHEMICALS WILL ACCOMPLISH CERTAIN PURPOSE WITHOUT NAMING ANY OTHERS OF CLASS TO WHICH IT BELONGS OR WITHOUT SO DESCRIBING THE SPECIES AND ITS MODE OF OPERATION AS TO CALL ATTENTION TO FACT THAT OTHER MEMBERS OF CLASS ARE ITS EQUIVALENTS AND WILL PERFORM SAME FUNCTIONS, HE IS NOT ENTITILED TO BROADER SCOPE OF DISCLOSED INVENTION BY CLAIMING WHOLE GROUP EVEN THOUGH THOSE SKILLED IN ART MAY KNOW THAT IN SOME RESPECTS AT LEAST DIFFERENT MEMBERS OF GROUP ARE EQUIVALENTS; CERTAIN MEMBERS OF WELL-DEFINED GROUP OF CHEMICALS MAY BE EQUIVALENTS FOR ONE PURPOSE AND NOT EQUIVALENT FOR ANOTHER". (*In re Soll*, 97 F.2d623, 38 USPQ

189 CCPA 1938, emphasis added). In the instant case, except the K562 cell line, the specification fails to disclose another species of the genus, K562 alone is not sufficient as the sole support of the starting material for the genus, and it is unpredictable and the instant disclosure fails to teach whether the results of the search will support the claimed genus. Appellants are reminded it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate written description.

Arguments concerning rejections of Claims 1-3, 5-7, 9-12, 17, 19, 20, 22-28, 40, 41, 50, 52 under 35 U.S.C. § 112, 1st paragraph, Enablement Requirement.

Appellants argue that whether or not a given human cell line naturally lacks MHC-I and MHC-II antigens is readily ascertainable using antibodies to determine MHC antigen expression or lack thereof. Appellants also argue that database searching for such cell lines and routine screening of cell lines, even if on a "large scale" basis, does not constitute undue experimentation (Brief, 3rd paragraph, page 7).

In response, in view of the disclosure of the specification, and the supplemental disclosure submitted by the appellants, so far, there is no evidence for the existence of another human cell line that lacks both MHC-I and MHC-II. Since only one cell line has been confirmed to be lacking both MHC-I and MHC-II antigens in the past 30 years, any future search of the kind may be proven to be strenuous and burdensome. Although the appellants insist that such cell lines could be readily searchable using antibodies, the specification fails to offer any guidance with respect to the starting point of the search.

For example, the specification fails to teach what normal human cell lines may possibly never have MHC-I & -II antigens, and what type of tumor cell lines may have higher possibilities of losing both MHC-I & -II antigens. In the end, it is unpredictable whether or not, and how many such cell lines could be identified. Except the K562 cell line, the specification fails to disclose another species of the genus, hence the skilled in the art intending to practice the invention has to first carry out undue experimentation to search for cell lines that meet claim limitation. Appellants are reminded it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement.

Appellants then argue unlike the specification at issue in the Genentech case law, the present specification teaches antibodies that can be utilized to establish the presence or absence of MHC antigen expression. Appellants cited *Engel Indus. Inc. v. Lockformer Co.* (CAFC 20 USPQ2d 1300), stating "The enablement requirement is met if the description enables any mode of making and using the invention"; and argue that since the specification provides a mode of practicing the invention, another species of a cell line in addition to the K562 is not required (Brief, paragraph bridging pages 8-9).

In response, the specification at issue is not analogous to the cited *Engel Indus. Inc. v. Lockformer Co.* case law, there the specification fails to disclose another form of connection for a system connecting the ends of sheet metal ducts. The court determines that the enablement requirement is separate from that of the best mode, and the enablement requirement is met if the description enables one mode of making and using the invention. However, in the instant case, the specification at issue is

whether disclosing a species is adequate description of the genus, and whether the disclosure provides sufficient guidance for making and using the genus cell lines. Here, except for the K562, the specification fails to provide any specific starting materials of the genus and any of the conditions for searching the genus, thus the Genentech case law still applies, wherein the court states,

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material** or of any of the conditions under which a process can be carried out, **undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

By disclosing antibodies that detecting MHC-I and MHC-II antigens, the specification only offers a mode of searching for the genus material required to practice the invention, and it sends the skilled in the art on a journey of strenuous hunt for which there is no guarantee of success, and it preempts the future before it has arrived. Accordingly the mode taught by the specification fails to meet the statutory enablement requirement.

Appellants also argue that the Examiner gives contradictory characterization of Ferrone et al and Wang et al under 35 U.S.C. § 112, 1st paragraph, and 35 U.S.C. § 103 (Brief, 2nd paragraph, page 9)

In response, this has been addressed in the advisory action, where the Examiner indicated that the provisions of 35 U.S. C. § 112 and 103 evaluates different aspects of a claim. *Ferrone* reference teaches the probabilities of losing MHC-I in 10% melanoma cell lines. It was cited under 35 U.S. C. § 112 to show that it is unknown and the specification fails to teach whether the 10% of the melanoma cell lines lost MHC-I and also lacking MHC-II antigen because *Winchester et al* teach widespread MHC-II expression in melanoma cell lines. On the other hand, *Ferrone* reference is relied upon under 35 U.S. C. § 103 because it teaches that certain melanoma cells do lack MHC-I and may lack MHC-II antigens as well. Thus, the Office is consistent in using the probabilities taught by *Ferrone et al* in the prosecution. In fact, although the rejection under 35 U.S. C. § 103 is withdrawn now, if the board determines that the probability theory holds as evidence for potential presence of a genus of cell lines that lack both MHC-I and MHC-II, the board should consider to re-instate the rejection under 35 U.S. C. §103, at least on the product claims.

Finally, concerning the claim recitation "defined medium", appellants argue the limitation is a preference not requirement (Brief, 3rd paragraph, page 9).

In response, the limitation of a claim is a requirement for the claim since the "preferred" language is not in the claim, the limitation is not to be read into the claim from the specification. Claims must, under modern claim practice, stand alone to define invention. Since, in patentability context, claims are to be given their broadest reasonable interpretations, and since limitations are not to be read

into claims from specification. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addressing the evidence cited by the Office showing that the culturing melanoma cell lines do need the presence of serum, appellants pointed out that melanoma cells can be weaned of their requirement for animal serum as a matter of routine experimentation. In response, such weaning was not in the original guidance, and melanoma cell lines are only an example for the broadly claimed genus of cell lines. Since the specification fails to teach the genus of defined media required for culturing the genus of various cell lines in addition to the K562 or melanoma cell lines, it would have required undue experimentation for the skilled to find out for themselves the defined medium required for practice the broadly claimed invention.

Arguments concerning the Double Patenting rejection of Claims 1-14, 17-28, 40-47, and 50-53.

Appellants indicated upon an indication of allowable subject matter, Appellants will submit a terminal disclaimer.

In response, until the filing of a terminal disclaimer, the rejection stands for reasons of record.

In conclusion, the Office has properly applied the methodology for determining the sufficiency or lack thereof for written description and enablement of the claimed invention as set forth under 35 U.S.C. § 112, 1st paragraph, and

established the claims on appeal lack of adequate written description and enablement.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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